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RELATIONSHIPS BETWEEN BLOOD FLOW AND SECRETION IN THE ISOLATED PERFUSED CANINE PANCREAS

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SUMMARY

1. Stimulation by a continuous intra-arterial infusion of secretin caused a marked vasodilatation in the pancreato-duodenal preparation or in the isolated pancreas perfused with whole heparinized blood. There was no difference in the vasomotor effects of two unequally purified preparations of secretin. The fact that the vasodilatation was still observed when the duodenum was removed proved that the haemodynamic effect of secretin was initiated in the pancreas itself.

2. The secretory response of the pancreas to a given dose of secretin was larger when the blood pressure was kept constant by increasing the blood flow than when the blood pressure was allowed to fall by maintaining the blood flow at a fixed value. It is concluded that the vasodilatation plays a role in the functional regulation of the pancreatic response to secretin.

3. The correlation between blood flow and arterial pressure on the one hand, and the secretory response to secretin on the other, was not mediated by the control of respiration since there was no variation in oxygen uptake in response to a variation in the blood flow. This correlation was still observed when the venous blood was discarded and therefore could not be explained by variations in the rate of recirculation of secretin. It was observed too in experiments where the duodenum was removed, the pancreas alone being introduced into the perfusion apparatus, which indicated that this effect was not mediated by a control of the release of secretin by the duodenum.

INTRODUCTION

The relationships between haemodynamic conditions and secretion in the exocrine pancreas are still largely obscure. Some secretory stimulants are known to produce vasomotor alterations (Gayet & Guillaumie, 1930;

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Jones, 1960; Delaney & Custer, 1965). However, it is not known whether these alterations are actually involved in the regulation of the secretory process.

Recent studies have developed the technique of perfusion of the isolated pancreas for the study of endocrine (Grodsky, Batts, Bennet, Vcella, MacWilliams & Smith, 1963; Sussman, Vaughan & Timmer, 1966), exocrine (Nardi, Greep, Chambers, MacCrae & Skinner, 1963; Case, Harper & Scratcherd, 1968; Hermon-Taylor, 1968) or both functions (Grenier, Gillet, Kachelhoffer, Wong, Barth, Randrianarivo, Stoebner, Weiss, Moody, Fries & Sundby, 1969) of the pancreas. This method seems particularly suited for the study of the correlation between blood flow and secretion, since haemodynamic parameters can be measured accurately and even modified independently of the mode of stimulation.

METHODS

Surgical procedure

In a fasting dog anaesthetized by intravenous Nembutal (0·5 mg/kg body wt.), the pancreas and attached duodenum (referred to as the pancreato-duodenal block) were removed following a technique described by Grenier, Gillet, Santizo, Klein, Barth, Oberling & Weiss (1967), with the difference that blood was perfused through the coeliac and superior mesenteric arteries (and not through the aorta) as described by Hermon-Taylor (1968). The procedure was completed by catheterization of the main pancreatic duct at the point where it pierces the duodenum. In some experiments, only the pancreas was preserved. In these cases, the duodenum was carefully dissected from the pancreas and discarded, except for a small piece of duodenal wall around the papilla of Vater, which could not be removed without damage to the pancreas.

Collection and storage of the blood

The blood was collected from one or more heparinized (3 mg/kg body wt., I.V.) donor dogs (anaesthetized with Nembutal, 0·5 mg/kg body wt., I.V.). If freshly collected blood was used for the perfusion of the pancreato-duodenal block, a more or less prolonged period of vasoconstriction was observed. If, however, the blood was stored for 3 to 4 hr at room temperature, the vasoactive principles (presumably catecholamines, secreted by the donor dog in response to bleeding) were inactivated. Glucose (0·4 g/l.) was added to the blood shortly before introduction into the circuit to compensate for the amount of glucose consumed by blood cells during the period of storage.

Technique of perfusion

The perfusion apparatus (Fig. 1) was primed with 500–600 ml. blood through a reservoir connected to the venous line. The blood was gassed with a mixture of 95 % O_2 and 5 % CO_2 in a disk oxygenator and then passed into the arterial line, via a Watson Marlow (MHRE Watson Marlow Ltd., Marlow, G.B.) flow inducer, through a bubble trap and a heat exchange coil maintained at 40° C in a water-bath.

When the pancreato-duodenectomy was complete, the pancreato-duodenal block (sixteen experiments) or the pancreas alone (seven experiments) was introduced into

the perfusion chamber, arterial and venous (portal) connexions made, and the perfusion was started. A solution of glucose, sodium and bicarbonate was continuously infused through the arterial line (Braun Ltd, Melsungen, West Germany) throughout the experiment, in order to maintain 'normal' values for blood glucose, alkaline reserve and the haematocrit. The rate of flow and the composition of this intra-arterial infusion differed, depending on whether the pancreato-duodenal block or the pancreas alone was introduced into the perfusion circuit:

	Pancreas + duodenum	Pancreas alone
Rate of perfusion (ml./hr)	45	30
Glucose (ml./hr)	0·50	0·50
$NaHCO_3$ (m-equiv/hr)	4	3

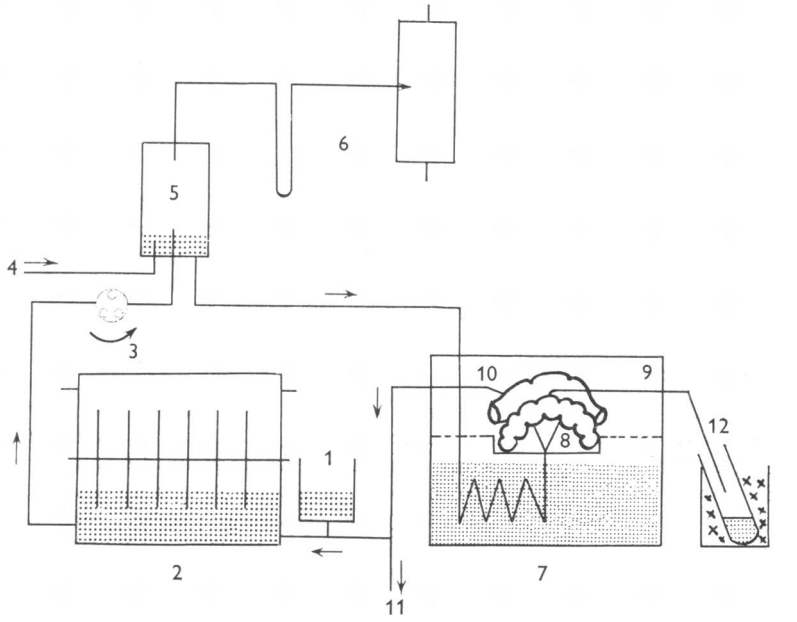

Fig. 1. Diagrammatic representation of the perfusion apparatus. 1: venous reservoir. 2: disk oxygenator. 3: perfusion pump on the arterial line. 4: continuous intra-arterial infusion of a solution of electrolytes, glucose, bicarbonate and secretin. 5: bubble-trap. 6: arterial pressure recording. 7: heat-exchange coil immersed in a water-bath at 40° C. 8: arterial endings connected with the coeliac trunk and the superior mesenteric artery. 9: perfusion chamber. 10: portal vein, connected with the venous line. 11: connexion used for the measurement of venous blood flow. 12: collection of the pancreatic juice.

Arterial blood pressure was continuously measured by means of a mercury manometer connected to the bubble-trap and recorded on a smoked drum. Blood flow was measured at intervals by collecting the venous outflow in 30-sec periods into a graduated tube. Arterial and venous pH, P_{O_2} and P_{CO_2} were measured at intervals.

Measurements of haematocrit, haemoglobin, glucose, bicarbonate, chloride, sodium, potassium, total protein and osmolality were made before the start and after the end of the experiment. These measurements constituted a control of homoeostasis and only the twenty-five experiments where these parameters were maintained between the values indicated below were used in this paper:

	Arterial	Venous
pH	7·18–7·46	7·10–7·45
P_{O_2} (mm Hg)	98–250	75–98
P_{CO_2} (mm Hg)	17–36	21–58
Haematocrit		22–47
Haemoglobin (g/100 ml.)		8·3–12·1
Glucose (g/l.)		1·20–2·20
Bicarbonate (m-equiv/l.)		15–29
Chloride (m-equiv/l.)		98–112
Sodium (m-equiv/l.)		129–154
Potassium (m-equiv/l.)		3·5–7·1
Total protein (g/l.)		47–81
Osmolality (m-osmole/kg)		282–330

Biopsies for histological and ultrastructural examination were performed immediately before the perfusion was discontinued. Duodenal secretions were discarded. Pancreatic juice was collected into graduated tubes maintained at 0° C in an ice bath. Volume and time of collection were recorded and bicarbonate, chloride and total protein concentrations were measured in all samples.

Experimental procedure

A period of 10–75 min was necessary to obtain a constant blood flow and to stabilize arterial pressure at about 80 mm Hg. Only then was stimulation started by adding secretin to the perfusion medium. Secretin was given at a constant dose in each experiment. Two kinds of secretin were used in this work; a relatively impure preparation (Boots secretin, Boots Pure Drug Co. Ltd. Nottingham, England), the dose of which is expressed as Crick, Harper & Raper, 1949, u./hr and a purer preparation (G.I.H. secretin, Gastro-intestinal hormones Research Unit, Chemistry Department, Karolinska Institutet, Stockholm, Sweden), the dose of which is expressed as clinical u./hr.

Three groups of experiments were performed.

Group 1. In fourteen experiments, the pancreato-duodenal block was used and the venous blood was recirculated (closed-circuit experiments). Stimulation was made with Boots secretin, 10 u./hr on three occasions, with Boots secretin, 20 u./hr on seven occasions, and with G.I.H. secretin, 20 clinical u./hr on four occasions.

Group 2. In seven experiments, the duodenum was discarded and only the pancreas was used, stimulation being made with G.I.H. secretin, 20 clinical u./hr. The venous blood was recirculated throughout the experiment (closed-circuit experiments).

Group 3. In two experiments, the pancreato-duodenal block was used, the pancreas being stimulated by G.I.H. secretin, 30 clinical u./hr. The venous blood was discarded as soon as stimulation was started (open-circuit experiments).

RESULTS

Influence of secretin on the vascular resistance

Group 1

Stimulation of pancreatic secretion by secretin caused a marked vasodilatation in the pancreato-duodenal block in all instances. In six experiments of this group, the blood flow was kept at the value it had before the onset of the stimulation for at least the first hour of the infusion of secretin.

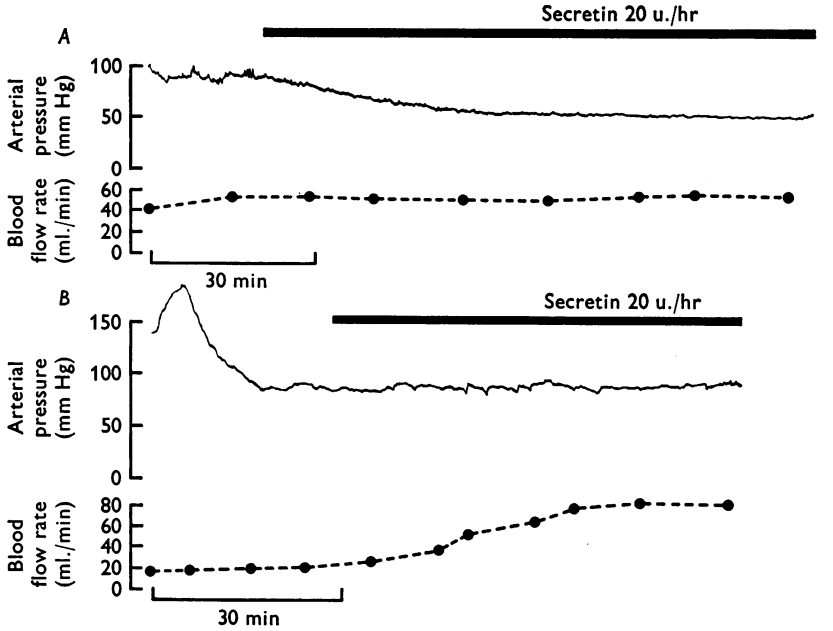

Fig. 2. Pancreato-duodenal blocks; closed-circuit experiments, stimulation with Boots secretin, 20 Crick, Harper & Raper u./hr. *A*: blood flow was maintained constant throughout the duration of the infusion of secretin. *B*: arterial pressure was kept at fixed value throughout the duration of the infusion of secretin. Horizontal bar represents the period of perfusion of secretin.

It was observed that the blood pressure fell regularly up to about 60 min and was then maintained at a more or less constant level between 25 and 50 mm Hg. Fig. 2*A* illustrates an experiment of this type.

In seven other experiments, the blood pressure was maintained constant (at about 80 mm Hg) during the first hour of the infusion of secretin, by progressively increasing the blood flow. Following this period of haemodynamic adjustment, the blood pressure remained approximately constant without further alteration in the blood flow. Fig. 2*B* illustrates an

experiment of this type. In these seven experiments the blood flow was generally more than doubled during the first hour of infusion of secretin (Fig. 3).

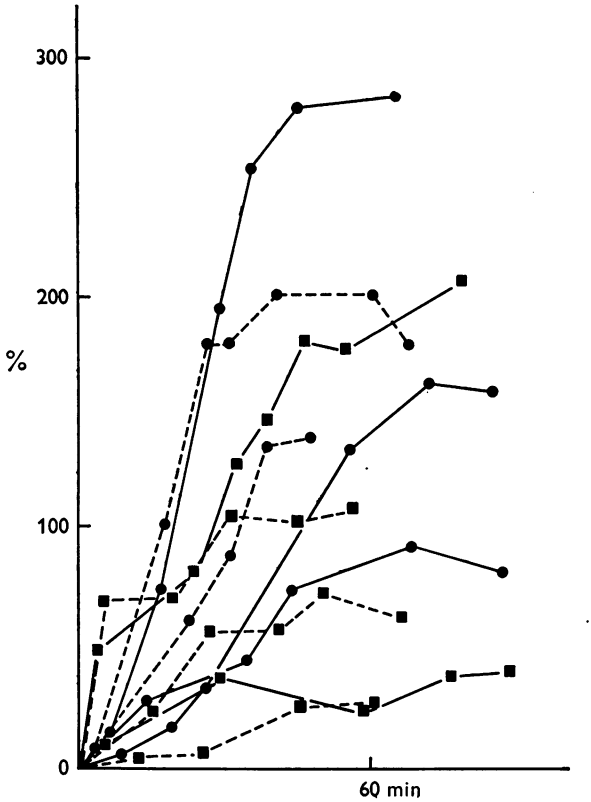

Fig. 3. Increase in blood flow (expressed as percentage of the blood flow at the onset of stimulation) observed during an infusion of secretin (started at zero time) in experiments where the arterial pressure was maintained at about 80 mm Hg.

Circles: experiments in pancreato-duodenal blocks; closed-circuit experiments, stimulation by Boots secretin at a dose of 10 (continuous line) and 20 (dashed line) Crick, Harper & Raper u./hr.

Squares: stimulation G.I.H. secretin by 20 clinical u./hr.

Continuous line: pancreato-duodenal blocks; closed-circuit experiments.

Dashed line: pancreas alone; closed-circuit experiments.

In both types of experiments in Group 1, secretin caused a progressive decrease in vascular resistance of the pancreato-duodenal block. Large differences in the decrease in vascular resistance were observed from one experiment to another; however, these differences could not be correlated with the type or with the dose of secretin.

Group 2

In Group 1 the duodenum accounted for at least 50% of the weight of the pancreato-duodenal block. Thus at least part of the haemodynamic alterations described in Group 1 might be attributed to the action of secretin on duodenal blood vessels. In seven experiments of Group 2, only the pancreas was perfused. Both types of experiments described in Group 1 were then repeated. In all instances the stimulation by secretin resulted in a decrease in vascular resistance in the isolated pancreas. In three out

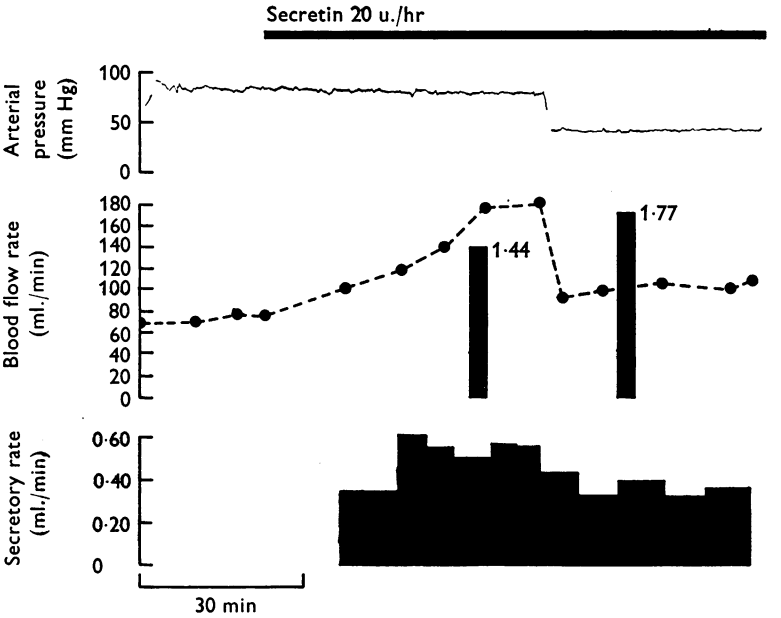

Fig. 4. Pancreato-duodenal block; closed-circuit experiment, stimulation by Boots secretin, 20 Crick, Harper & Raper u./hr (horizontal bar). After a period when arterial pressure was kept at about 80 mm Hg, the blood flow was reduced in order to stabilize the blood pressure at about 40 mm Hg. Vertical bars: oxygen consumption (ml./min).

of these seven experiments, arterial pressure was maintained at about 80 mm Hg. In the first hour after infusing secretin, the blood flow was generally less than double the control values (Fig. 3). Large differences, however, occurred between different experiments.

Influence of haemodynamic conditions on the secretory rate of the pancreas

In order to study the influence of haemodynamic conditions on the secretory response to secretin, the arterial pressure was purposely altered

after the vascular resistance had reached a stable level, generally during the second hour of stimulation. The rate of infusion of secretin was unchanged.

Group 1

In two experiments, arterial pressure was maintained constant at 80 mm Hg during the infusion of secretin until a plateau of blood flow and of the rate of secretion was reached. Then, the arterial pressure was reduced to 40 mm Hg within one minute by reducing the blood flow and the

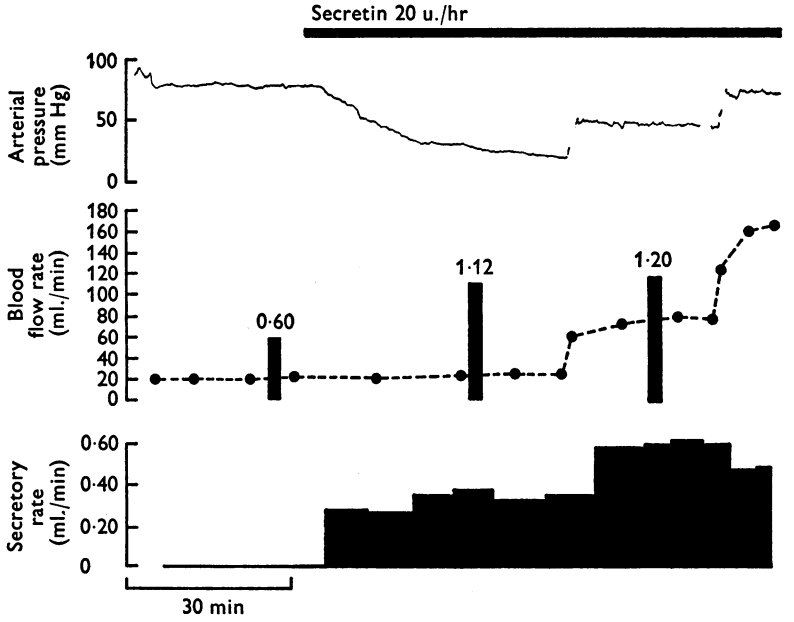

Fig. 5. Pancreato-duodenal block; closed-circuit experiment, stimulation by Boots secretin, 20 Crick, Harper & Raper u./hr. After a period of perfusion at a constant blood flow, the arterial pressure was raised to 50 mm Hg and then to 80 mm Hg, by increasing the blood flow. Same symbols as in Fig. 4.

effects on the rate of secretion were observed. In four contrasting experiments, the blood flow was maintained constant at the value it had just before the onset of stimulation by secretin until a plateau of arterial pressure and of secretion rate were obtained. Then the arterial pressure was increased to 80 mm Hg by increasing the blood flow, and the effects on the secretory rate of pancreatic juice were observed. In both groups of experiments it was seen that any alteration in the blood pressure was followed by a variation in the secretory rate in the same direction. Figs. 4 and 5 show the results obtained in two experiments.

Measurements of oxygen consumption indicated that the infusion of secretin resulted in an increase in oxygen uptake. However, no relationship could be found between oxygen uptake and the blood flow, neither in the entire group nor in a single experiment. These facts suggest that, under the conditions of this work, the influence of haemodynamic conditions on the secretory response of the pancreas to secretin was not mediated through the regulation of the respiratory process.

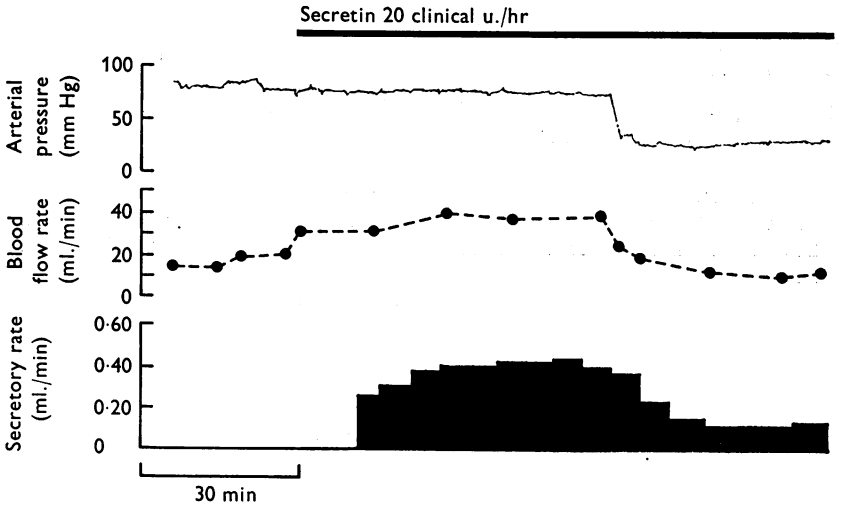

Fig. 6. Pancreas alone; closed-circuit experiment, stimulation by G.I.H. secretin, 20 clinical u./hr. After a period when arterial pressure was kept at about 80 mm Hg, the blood flow was reduced in order to stabilize the blood pressure at about 40 mm Hg.

Group 2

The secretory rate of the juice was lower in this group than in those experiments in Group 1 where the stimulation was of the same magnitude (G.I.H. secretin, 20 clinical u./hr). However, stable rates of flow of juice were obtained in all experiments in Group 2, and it was observed that alterations in the blood pressure were followed by variations in the secretory rate of the same type as those described for Group I. Thus it could be assumed that the variation in the secretory response of the pancreas was produced by a variation in the haemodynamic condition within the pancreas itself. Figs. 6 and 7 show the results obtained in two experiments.

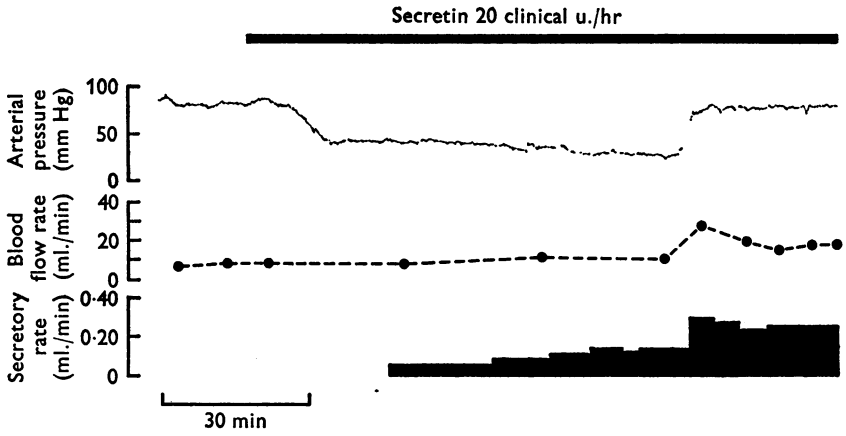

Fig. 7. Pancreas alone; closed-circuit experiment, stimulation by G.I.H. secretin, 20 clinical u./hr. After a period of perfusion at a constant blood flow, the arterial pressure was raised to 80 mm Hg by increasing the blood flow.

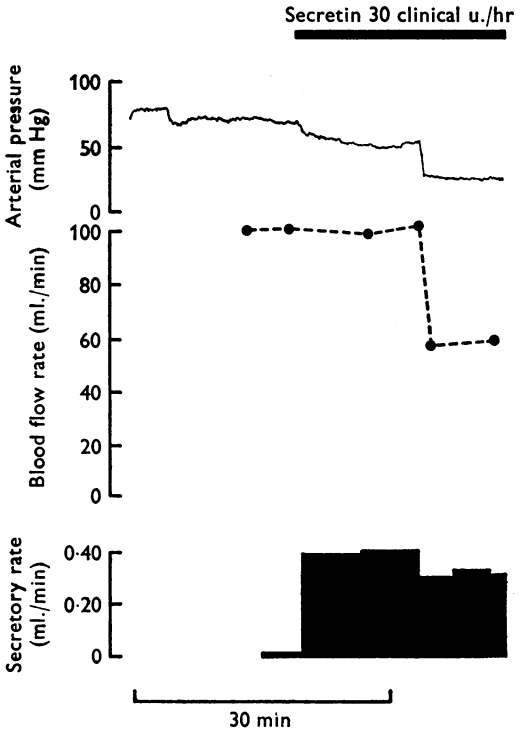

Fig. 8. Pancreato-duodenal block; venous effluent was discarded throughout the period of stimulation by G.I.H. secretin, 30 clinical u./hr. After a period when the blood flow was maintained at a fixed value, it was then reduced in order to stabilize the blood pressure at about 30 mm Hg.

Group 3

The pancreas in the experiments in Groups 1 and 2 described above were subjected to the action of secretin from two sources, the secretin which was infused into the circulation at a constant rate and that which escaped destruction after passage through the pancreas and was re-circulated. The rate at which secretin reached the pancreas was influenced by the blood flow. In order to elucidate the part played by the re-circulation of secretin, two experiments were performed in which the

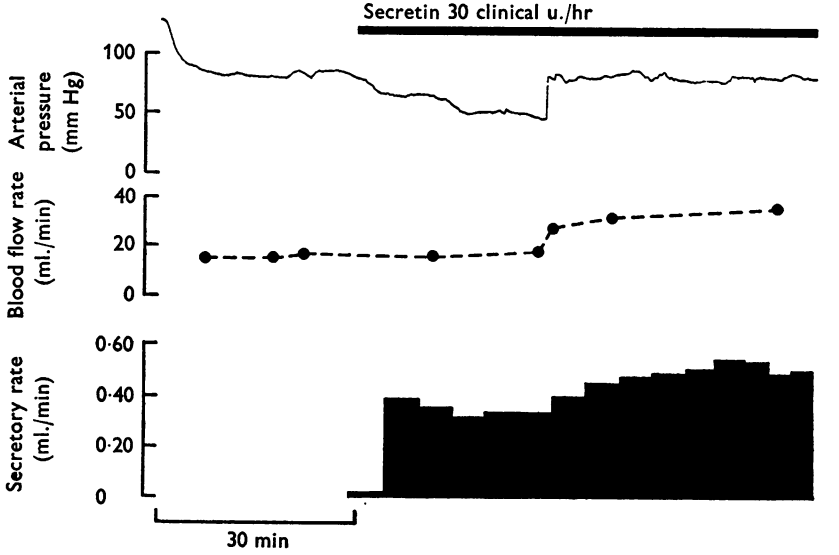

Fig. 9. Pancreato-duodenal block; venous effluent was discarded throughout the period of stimulation by G.I.H. secretin, 30 clinical u./hr. After a period when the blood flow was kept constant, the arterial pressure was raised to 80 mm Hg by increasing the blood flow.

venous effluent was allowed to go to waste. Under these latter conditions, haemodynamic changes influenced the secretory response to secretin as in the experiments in which secretin re-circulation occurred (Figs. 8 and 9). Thus re-circulation of secretin played no significant part in these responses. In Fig. 10 all the experiments of the different groups are illustrated; it can be seen that the secretory response of the pancreas was greater when the arterial pressure was maintained at 80 mm Hg than when it was allowed to fall to between 50 and 25 mm Hg.

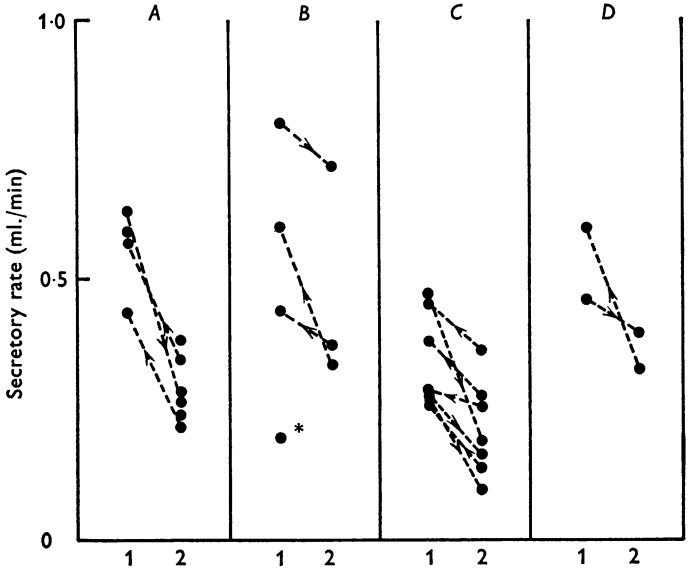

Fig. 10. Mean rate of flow of pancreatic juice (secretory rate, ml./min) in experiments where the arterial pressure was kept at about 80 mm Hg at one period (1), and where it was allowed to fall to between 25 and 50 mm Hg at another period in the same experiment (2). Dashed lines between data obtained from a single experiment. The direction of the arrows indicates the variation in arterial pressure in those experiments where conditions (1) and (2) were successively achieved.

A: pancreato-duodenal blocks; closed-circuit experiments, stimulation by Boots secretin, 20 Crick, Harper & Raper u./hr.

B: pancreato-duodenal blocks; closed-circuit experiments, stimulation by G.I.H. secretin, 20 clinical u./hr. Asterisk denotes an experiment where the pancreas failed to secrete properly as a result of intravascular coagulation.

C: pancreas alone; closed-circuit experiments, stimulation by G.I.H. secretin, 20 clinical u./hr.

D: pancreato-duodenal blocks; venous effluent discarded throughout the period of stimulation by G.I.H. secretin, 30 clinical u./hr.

DISCUSSION

The effect of gastrointestinal hormones on pancreatic blood flow has been the subject of many studies leading to conflicting results. Several authors have described a vasodilating effect of secretin on the pancreas (Gayet & Guillaumie, 1930; Holton & Jones, 1960; Hermon-Taylor, 1968; Hickson, 1970) whereas this effect was not encountered in other studies (Weaver, 1928; Hilton & Jones, 1963). It has been claimed that the vasodilating effect of secretin depended on the effect of the hormone on the pancreatic duct pressure (Bennet & Still, 1933), the degree of purity of the

hormone (Hilton & Jones, 1968), the number of injections (Lingren, 1958) or the time of the injection of secretin in the course of an experiment (Aune & Semb, 1969). This question has been fully discussed by Barlow, Greenwell, Harper & Scratcherd (1968). In our experiments two kinds of secretin were used, with roughly the same potent vasodilator influence on the pancreato-duodenal block. This was in good agreement with observations made by Aune & Semb (1969) in the dog but not with findings described in the cat by Hilton & Jones (1968). Such a discrepancy could be explained by the fact that the purest preparation of secretin used in our work (75 clinical units in 35 μg) was less pure than that of Hilton & Jones (1968), which had no action on a pancreatic blood flow (75 clinical units in 6 μg). The hormonal preparation used by Aune & Semb (1969) was claimed to be pure, but the ratio of clinical units to weight was not given.

The fact that the vasodilating property of secretin was still present when the duodenum was discussed indicates that the vasoactive mechanism is initiated within the pancreas itself.

The influence of vasomotor reactions in the pancreas on the secretory function of the gland is still an open question. It has been suggested that, above a critical level, blood flow does not interfere with the secretory response to stimulants (Tankel & Hollander, 1957). However, it is logical to suppose that any increase in blood flow will raise the amount of stimulant flowing into the pancreas (Thomas, 1967). Experiments to date have failed to demonstrate that haemodynamic conditions were causally related to the secretory agent (Nardi *et al.* 1963; Hermon-Taylor, 1968; Aune & Semb, 1969). Under the conditions of our experiments, a variation in blood flow was always followed by a variation in the secretory response to secretin. Recently, Rao & Elmslie (1970) have described a technique of perfusing the pancreas with all the duodenum removed. The addition of Boots secretin to this preparation did not produce a fall in perfusion pressure. This we have not been able to confirm. However, the experiments of Rao & Elmslie (1970) were not performed with whole blood, but with blood which had an haematocrit as low as 10 in some instances.

Observations made in experiments where the duodenum was discarded showed that changes in the blood flow did not influence the secretory rate of pancreatic juice by releasing endogenous secretin or some other secretory or anti-secretory agent from the duodenal mucosa. The work of Nardi *et al.* (1963) and of Hermon-Taylor (1968) has shown that a low arterial pressure in an isolated perfused pancreas is compatible with adequate perfusion and respiration of the gland. In our experiments, oxygen consumption under stimulation by secretin always remained above the value it had before the onset of the stimulation, even when the blood pressure was allowed to fall to between 25 and 50 mm Hg, confirming the

finding that blood flow and oxygen consumption can be dissociated in exocrine glands (Terroux, Sekelj & Burgen, 1959). Thus, the reduction in the secretory rate under these conditions compared with the value it had when the blood pressure was maintained at 80 mm Hg cannot be accounted for by hypoxia. In addition, observations made in open-circuit experiments make it unlikely that the relationship between haemodynamic conditions and the secretory response to secretin is due to variation in the rate of perfusion of recirculated secretin.

In conclusion, since any fall in vascular resistance is not *in vivo* followed by a fall in arterial pressure, an increase in blood flow will result, and it is suggested that any vasodilatation enhances quantitatively the secretory response of the exocrine pancreas to secretin.

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REFERENCES

AUNE, S. & SEMB, L. S. (1969). The effect of secretin and pancreozymin on pancreatic blood flow in the conscious and anaesthetized dog. *Acta physiol. scand.* **76**, 406–414.

BARLOW, T. E., GREENWELL, J. R., HARPER, A. A. & SCRATCHERD, T. (1968). Factors influencing pancreatic blood flow. In *Blood Flow through Organs and Tissues*, pp. 469–484, ed. BAIN, W. H. & MURRAY HARPER, A. Edinburgh and London: E. and S. Livingston.

BENNET, A. L. & STILL, E. U. (1933). A study of the relation of pancreatic duct pressure to the rate of blood flow through the pancreas. *Am. J. Physiol.* **106**, 454–459.

CASE, R. M., HARPER, A. A. & SCRATCHERD, T. (1968). Water and electrolyte secretion by the perfused pancreas of the cat. *J. Physiol.* **196**, 133–149.

CRICK, J., HARPER, A. A. & RAPER, H. S. (1949). On the preparation of secretin and pancreozymin. *J. Physiol.* **110**, 367–376.

DELANEY, J. P. & CUSTER, J. (1965). Gastrointestinal blood flow in the dog. *Circulation Res.* **17**, 394–402.

GAYET, R. & GUILLAUMIE, M. (1930). Les réactions vaso-motrices du pancréas étudiées par la mesure des débits sanguins. *C. r. Séanc. Soc. Biol.* **103**, 1106–1110.

GRENIER, J. F., GILLET, M., KACHELHOFFER, J., WONG, P., BARTH, A. M., RANDRIANARIVO, P., STOEBNER, P., WEISS, A. G., MOODY, A. J., FRIES, A. S. & SUNDBY, F. (1969). Circulation extra-corporelle du massif duodéno-pancréatique chez le chien. Technique. Fonctionnement. Intérêt. *Ann. Chir. Thor. Car.* **8**, 349–360.

GRENIER, J. F., GILLET, M., SANTIZO, G., KLEIN, A., BARTH, A. M., OBERLING, F. & WEISS, A. G. (1967). Les greffes du pancréas chez le chien. Etude de la survie et des potentialités fonctionnelles du transplant. *Annls Chir.* **21**, 1523–1537.

GRODSKY, G. M., BATTS, A. A., BENNET, L. L., VCELLA, C., MACWILLIAMS, N. B. & SMITH, D. F. (1963). Effects of carbohydrates on secretion of insulin from isolated rat pancreas. *Am. J. Physiol.* **205**, 638–644.

HERMON-TAYLOR, J. (1968). A technique for perfusion of the isolated canine pancreas. Responses to secretin and gastrin. *Gastroenterology* **55**, 488–501.

HICKSON, J. C. D. (1970). The secretory and vascular response to nervous and hormonal stimulation in the pancreas of the pig. *J. Physiol.* **206**, 299–322.

HILTON, S. M. & JONES, M. (1963). Plasma kinin and functional vasodilatation in the pancreas. *J. Physiol.* **165**, 35–36*P*.

HILTON, S. M. & JONES, M. (1968). The role of plasma kinin in functional vasodilatation in the pancreas. *J. Physiol.* **195**, 521–533.

HOLTON, P. & JONES, M. L. (1960). Some observations on changes in the blood content of the cat's pancreas during activity. *J. Physiol.* **150**, 479–488.

JONES, M. L. (1960). The effect of secretin on pancreatic blood flow. *J. Physiol.* **151**, 49–50.

LINGREN, P. (1958). An improved method for drop recording of arterial or venous blood flow. *Acta physiol. scand.* **42**, 5–11.

NARDI, G. L., GREEP, J. M., CHAMBERS, D. A., MACCRAE, C. & SKINNER, P. B. (1963). Physiologic peregrinations in pancreatic perfusion. *Ann. Surg.* **158**, 830–839.

RAO, M. M. & ELMSLIE, R. G. (1970). A modified technic of isolated pancreatic perfusion. *J. surg. Res.* **10**, 357–362.

SUSSMANN, K. E., VAUGHAN, G. D. & TIMMER, R. F. (1966). An *in vitro* method for studying insulin secretion in the perfused isolated rat pancreas. *Metabolism* **15**, 466–476.

TANKEL, H. J. & HOLLANDER, F. (1957). The relation between pancreatic secretion and local blood flow. A review. *Gastroenterology* **32**, 633–641.

TERROUX, K. G., SEKELJ, P. & BURGEN, A. S. V. (1959). Oxygen consumption and blood flow in the submaxillary gland of the dog. *Can. J. Biochem. Physiol.* **37**, 5–15.

THOMAS, J. E. (1967). Neural regulation of pancreatic secretion. In *Handbook of Physiology*, Alimentary Canal, vol. II, pp. 955–968. Washington, D.C.: American Physiological Society.

WEAVER, M. M. (1928). Studies on the visceral vaso motor responses to intravenous injections of purified pancreatic secretin. *Am. J. Physiol.* **85**, 410–411.